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Low Grade Central Osteogenic Sarcoma

A Long-Term Followup of 20 Patients

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Osteogenic sarcoma is a heterogeneous family of tumors that has a variable biologic behavior. Low grade central osteogenic sarcoma is an uncommon form that is characterized by a long premorbid history and is compatible with prolonged survival after treatment. Twenty cases of low grade central osteosarcoma with long-term followup (16 [2.5–48] years) were studied retrospectively. The age distribution was broad (range, 15–83 years). All tumors arose in the lower limb. The primary symptom was pain; mean duration was 44 months (range, 1–180 months). A diagnosis of low grade central osteosarcoma was made primarily for 11 patients. For 9 others, fibrous dysplasia (3), nonossifying fibroma (2), fibroma (1), chondromyxoid fibroma (1), chondrosarcoma (1), and simple bone cyst (1) were diagnosed initially. Intralesional surgery was associated with recurrence in every case. Radical margins were not associated with local recurrence. Four recurrences were higher grade and 1 was dedifferentiated. Three of 4 patients with metastases died of their disease. Five- and 10-year survival was 90% and 85%, respectively. Histology and radiology are complementary for confirming the diagnosis. Low grade central osteosarcoma seems to be controllable by surgery alone if at least wide margins are used.

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Osteosarcoma classically is regarded as a high grade malignancy of which several histologic types (osteoblastic, chondroblastic, and fibroblastic) can be distinguished from their dominant matrix patterns. Subtypes also have been recognized, including malignant fibrous histiocytoma-like,[1] telangiectatic,[14] and giant cell-rich[16] variants. However, there is a well-differentiated variant, termed low grade central osteosarcoma, that often is mistaken for a benign fibrous lesion and that is attended by a more favorable survival than conventional osteosarcoma.[13,21] Only a few individual cases of this rare primary tumor have been described.[2,9,19,20,23]

This study updates followup information on 20 examples of low grade osteosarcoma in patients from 1 institution.

STUDY GROUP AND METHODS

From 1919 to 1994, 20 patients with low grade osteosarcoma either were referred to the Mayo

Clinic for diagnosis and management of their primary tumor, or presented after local recurrence was detected following an earlier procedure in which the diagnosis of low grade central osteosarcoma was not recognized (Table 1). The histologic slides (stain, hematoxylin and eosin) were reviewed for all 20 cases and the diagnosis confirmed. The clinical records of all patients were available for review. Data pertaining to 15 of these patients have been described in an earlier report.[13] The total number of patients in the Mayo Clinic files with osteosarcoma during the same period as these patients was 1649.

There was an equal number of men and women. The peak incidence occurred during the third decade (range, 15–83 years). The majority presented with spontaneous onset of pain; the mean duration of symptoms was 44 months (range, 1–180 months). All tumors arose in the lower extremity, and most were about the knee. One arose at the ankle and another at the hip. The mean tumor size was 7.5 cm (range, 3.5–13 cm) as recorded from radiographs or from pathologic specimens. No record of size was noted for 3 patients.

The tumors were clinically staged (Table 2) according to the criteria proposed by Enneking,[6] and of the 20 tumors, 16 were Stage IA (low grade intracompartmental) at presentation, and 4 were Stage IB (low grade extracompartmental). Eleven patients had surgery for their primary tumor done at the Mayo Clinic (4 intralesional, 1 marginal, 2 wide, and 4 radical margin); 3 patients had radiotherapy, and 8 had surgery done elsewhere (8 intralesional). One patient referred to the Mayo clinic refused surgery and was treated with radiotherapy only. No patient received chemotherapy.

There were 14 local recurrences. Low grade central osteosarcoma was diagnosed in 6 patients (1 at Mayo, 5 outside) after a recurrence developed. All 14 local recurrences were treated at the Mayo Clinic, and all except 1 were treated with amputation. The 1 patient who did not have amputation for local recurrence was treated with a wide resection followed by reconstruction with an intercalated allograft. In 4 patients, confirmed distant metastases developed; one patient who died without treatment of his primary tumor was presumed to have succumbed to metastatic disease.

TABLE 1. Clinical Data on 20 Patients With Low Grade Central Osteogenic Sarcoma

Case	Age/Gender	Site	Presentation	Duration of Symptoms (months)	Size (cm)
1	23/Male	Femur/epiphysis/distal	Pain, mass	84	?
2	42/Male	Femur/epiphysis/distal	Pain	30	?
3	29/Female	Femur/epiphysis/distal	Pain	12	5
4	28/Male	Femur/greater trochanter	Pain	4	7
5	62/Female	Tibia/metaphysis/proximal	Mass	180	7
6	24/Male	Femur/epiphysis/distal	Pain	0	?
7	28/Male	Femur/epiphysis/distal	Pathologic fracture	0	5
8	24/Male	Tibia/metaphysis/proximal	Pain	60	10
9	20/Female	Tibia/metaphysis/proximal	Pain	0	9
10	23/Female	Femur/epiphysis/distal	Pain	12	6
11	52/Male	Tibia/metaphysis/proximal	Pain	0	0
12	83/Female	Fibula/epiphysis/distal	Mass	36	4
13	25/Female	Femur/epiphysis/distal	Pain	0	3.5
14	15/Male	Tibia/metaphysis/distal	Pain	1	12
15	64/Female	Tibia/metaphysis/proximal	Pain	18	10
16	16/Female	Femur/metaphysis/distal	Pain	0	6
17	28/Male	Femur/metaphysis/distal	Pathologic fracture	0	4
18	30/Female	Femur/metaphysis/distal	Pain	36	13
19	25/Male	Femur/metaphysis/distal	Pain	12	8
20	23/Female	Tibia/metaphysis/distal	Pain	84	11

TABLE 2. Treatment and Local Recurrence

Case	Stage	Index Surgery	Adjuvant Treatment	Recurrence (months)	Treatment of Recurrence
1	IB	Curettage and bone graft	None	Yes/27	Amputation
2	IA	None	Radiotherapy		
3	IB	Curettage and bone graft	Radiotherapy	Yes/135	Amputation
4	IA	Curettage and bone graft	None	Yes/3	Disarticulation
5	IB	Marginal excision and bone graft	None	Yes/135	Amputation
6	IA	Curettage and bone graft	None	Yes/168	Amputation
7	IB	Curettage and bone graft	None	Yes/78	Amputation
8	IA	Curettage and bone graft	Radiotherapy	Yes/6	Amputation
9	IA	Intralesional amputation	None	Yes/11	Amputation
10	IA	Curettage and bone graft	Radiotherapy	Yes	Amputation
11	IA	Curettage and bone graft	None	Yes	Amputation
12	IA	Curettage and bone graft	None	Yes/132	Amputation
13	IA	Wide excision	None	No	
14	IA	Radical amputation	None	No	
15	IA	Radical amputation	None	No	
16	IA	Curettage and bone graft	None	Yes/13	Amputation
17	IA	Curettage and bone graft	None	Yes/54	Limb salvage
18	IA	Radical amputation	None	No	
19	IA	Wide excision	None	Yes/22	Amputation
20	IA	Radical amputation	None	No	

The median followup after surgery was 14.4 years (range, 2.4–48.1 years) (Table 3). At last followup, 4 were dead with no evidence of disease, 4 had died from disease, and 12 were alive with no evidence of disease. Of the 12 patients who were living, followup of 1 patient (80 months) occurred on a regular basis, whereas information regarding the remaining 11 was obtained from the Mayo Clinic Tumor Registry, which provides a yearly update of all patients treated for sarcoma at this institution. Specific questionnaires pertaining to the patient's health, cancer status, and any treatment or complications are forwarded to the patient, and followup telephone calls are made to the patient or letters are sent to the patient's local doctor if a reply is not received within a certain period. No patients were lost to followup.

Statistics

Differences between categories were analyzed using contingency tables (Table 4). Differences between continuous variables were analyzed using the Mann–Whitney test for nonparametric groups. Overall survival was calculated from the time of diagnosis to death from tumor. Deaths from causes other than tumor were not included in the study. A probability <0.05 was regarded as significant.

RESULTS

Primary diagnoses of osteosarcoma were made for 11 patients (9 at Mayo, 2 outside) and chondrosarcoma for 1 patient (outside); the original diagnosis for 8 patients was of benign processes: 2 nonossifying fibromas (both outside), 3 fibrous dysplasia (2 Mayo, 1 outside), 1 fibroma (Mayo), 1 chondromyxoid fibroma (outside), 1 simple cyst (outside).

Radiographic Appearance

The radiographic features of low grade central osteosarcoma are variable. They are usually large medullary tumors in the end of a long bone. Trabeculation was a common finding, and involved part or all the tumor (Fig 1A). Sclerosis was seen in almost all cases, and when it involved the rim of the tumor, it varied in thickness (Fig 1B). Periosteal new bone formation and soft tissue

TABLE 3. Followup and Clinical Outcome

Case	Metastasis	Followup (months)	Status at Followup
1		316	Dead, no evidence of disease
2		42	Dead with disease
3		577	Dead, no evidence of disease
4		29	Dead, no evidence of disease
5		259	Dead, no evidence of disease
6	Pelvic nodes	237	Dead with disease
7		171	Alive, no evidence of disease
8		153	Alive, no evidence of disease
9	Ilium, pubis	153	Alive, no evidence of disease
10		242	Alive, no evidence of disease
11		251	Alive, no evidence of disease
12		175	Alive, no evidence of disease
13		223	Alive, no evidence of disease
14		107	Alive, no evidence of disease
15	Pulmonary	135	Dead with disease
16		213	Alive, no evidence of disease
17		187	Alive, no evidence of disease
18		164	Alive, no evidence of disease
19	Base of skull	69	Dead with disease
20		80	Alive, no evidence of disease

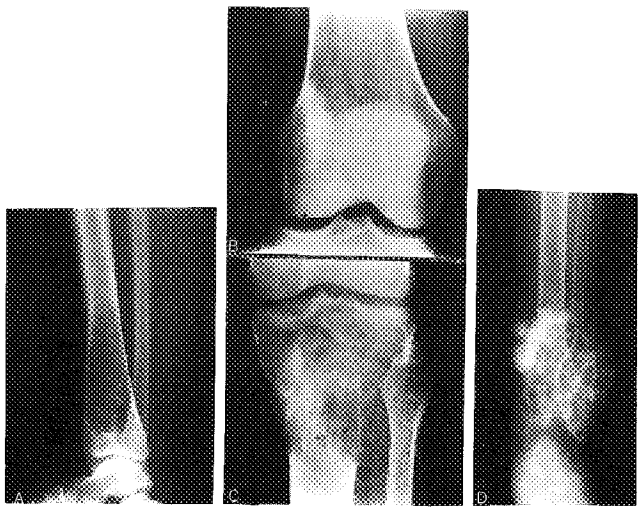

Fig 1A–D. (A) A 23-year-old woman presented with a 7-year history of lower leg pain. Note intramedullary location and trabeculated character of tumor. Her initial clinical diagnosis was fibrous dysplasia, but a biopsy specimen showed low grade central osteogenic sarcoma. She had below knee amputation and is alive and disease free 6.7 years after surgery. (B) A 25-year-old woman presented with sudden onset of knee pain. Radiographs showed an eccentric lesion with a thickened rim of peritumoral sclerosis in the lateral femoral condyle. She had wide excision of the tumor and remains disease free 18.5 years after surgery. (C) A 52-year-old man presented with a short history of tibial pain. Radiographs showed a mixed lytic and sclerotic lesion in the meta-epiphyseal region of the tibia. Initial diagnosis was chondromyxoid fibroma. He was treated with curettage and bone grafting, but the lesion recurred. Review of the initial histology and that of the recurrence showed low grade central osteosarcoma. He had an above knee amputation and is alive without disease after 20 years. (D) An 83-year-old patient presented with a 3-year history of a mass and discomfort about the ankle. Radiographs showed an aggressive process involving the fibula and tibia. Note the destruction of the fibula with a prominent sunburst-like periosteal reaction, and the calcified lobulated soft tissue extension medial to the tibia. This patient was first treated with an intralesional excision elsewhere before a local recurrence developed that was treated with a below-knee amputation. She remains disease free 14.8 years after surgery.

TABLE 4. Host and Tumor Variables Related to Local Recurrence*

Variable	Local recurrence		P Value
	Yes	*No*	
Number	14	5	
Mean age (year)	33 (16–83)	31 (15–64)	
Gender			
Male	8	1	0.2
Female	6	4	
Mean size (range) cm	6.4 (4–10)	10 (3.5–13)	0.06
Location			
Upper leg	9	2	0.4
Lower leg	5	3	
Proximal	5	1	0.5
Distal	9	4	
Stage			
IA	8	5	0.08
IB	6	0	
Margin			
Intralesional	12	0	0.0009
Marginal	1	0	
Wide	1	1	
Radical	0	4	

* Data for 19 patients. One patient was excluded because no surgical treatment was given.

extension usually were absent, although more aggressive behavior sometimes was characterized by breaching of the cortex and periosteal reaction with new bone oriented parallel to the cortex or in a sunburst pattern (Fig 1C). Occasionally, areas of dense mineralization and lobulation also could be observed within the tumor (Fig 1D). Extracompartmental extension, if present, was recognized by ill-defined soft tissue opacities opposite areas of cortical irregularity. Pathologic fracture was observed in 2 cases.

Macroscopic Appearance

The macroscopic appearance was consistent with a slowly growing lesion, a large well-demarcated mass with associated expansion or erosion of the adjacent endosteum. In 6 cases, the tumor had breached the cortex and had infiltrated the overlying soft tissue. The tumor was of a firm gritty consistency and lacked the fish-flesh appearance of a high grade sarcoma.

Microscopic Appearance

In general, the histology of low grade central osteosarcomas was characterized by populations of spindle-shaped cells arranged in interlacing bundles or a herringbone pattern (Fig 2A) and whose nuclei were minimally hyperchromatic and irregular in shape or size, and showed scattered but scarce mitotic figures (Fig 2B). The matrix often consisted of bundles of collagen fibers separating groups of neoplastic cells. Seams of tumor osteoid were evident, although the amount was variable (Fig 2C). The key differentiating factor for low grade central osteogenic sarcoma from benign conditions such as fibrous dysplasia was a permeative character to the sheets of tumor cells that in some areas appeared to surround bony trabeculae or permeated marrow fat (Fig 2D). Rarely, the tumor destroyed the cortex to invade soft tissues.

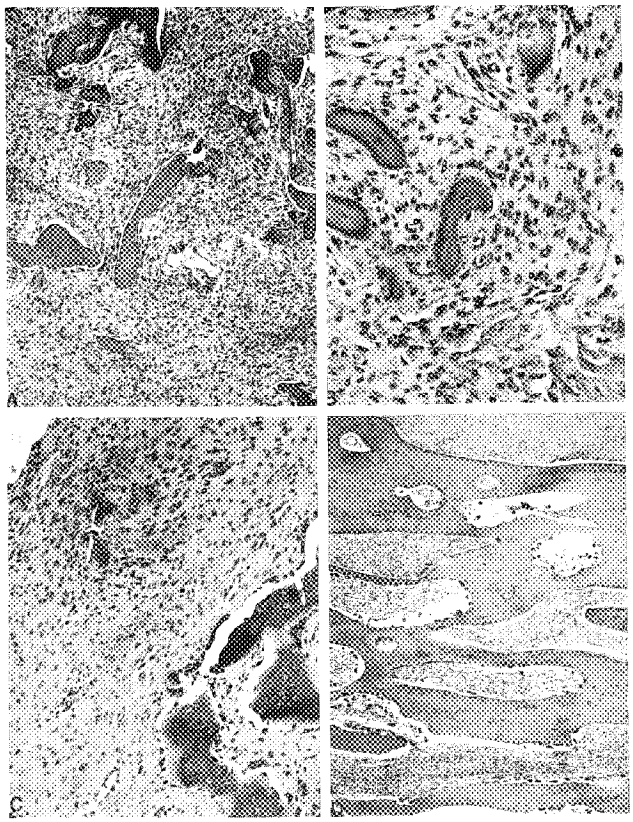

Fig 2A–D. Low grade central osteogenic sarcoma is characterised by (A) interlacing sheets of spindle-shaped cells (stain, hematoxylin and eosin; original magnification, ×160), (B) with nuclei that are minimally irregular in shape and size, scarce mitoses (stain, hematoxylin and eosin; original magnification, ×250), and (C) variable amounts of osteoid seams (stain, hematoxylin and eosin; original magnification, ×160). (D) The key differentiating feature of low grade central osteosarcoma from other apparently benign lesions is the marrow permeation of spindle cells between the trabeculae.

Local Recurrence

Local recurrence developed at a median time of 35.4 months (range, 3–168 months) after surgery. No tumors treated with radical margins recurred. Intralesional surgery that consisted of curettage and bone grafting was associated with recurrence in every case. In all 3 patients who received radiotherapy as an adjunct to intralesional surgery, local recurrence developed. The radiation protocol and technique differed in each case (treatment years, 1925, 1966, 1973). One patient who only received radiotherapy for his tumor was not included in the analysis of local recurrence (treatment year, 1920).

There were trends suggesting that extracompartmental or smaller primary tumors were more likely to recur. Gender and primary tumor location did not correlate with local recurrence.

Of the 14 local recurrences, 4 recurred with a higher grade and 1 dedifferentiated; the remainder retained the histologic appearances of their parent tumor.

Metastasis

Four patients had confirmed metastases (2 osseous, 1 lymph node, 1 pulmonary). These developed 17, 50, 97, and 236 months after diagnosis. Two metastases occurred after high grade local recurrences developed; a third patient did not have a local recurrence before metastases developed. These 3 patients died from their disease. In a fourth patient, a distant metastasis developed in the ilium, which was treated successfully with a hindquarter amputation. This had been the donor site of initial bone graft, and therefore local contamination also was considered a possibility, in addition to metastasis. A fifth

patient had refused surgical treatment of his primary lesion and died 42 months later. No autopsy or staging studies were done on this patient to confirm metastasis, although this was assumed to be the cause.

The 5- and 10-year survival rates were 90% and 85%, respectively (Fig 3).

DISCUSSION

Osteosarcoma is a heterogeneous family of tumors consisting of osteoblastic, chondroblastic, myofibroblastic, and fibrohistiocytic cell populations.[4,8] Low grade central osteosarcoma appears to be a distinct member of this group which is characterized by a more favorable clinical outcome than conventional osteosarcoma. Various studies have alluded to such an entity by showing a better prognosis for those tumors designated as being Grade I, even though different criteria for grading were used and specific attempts to differentiate histologic subtypes were not made.[3,18] In contrast, several authors have recommended that osteosarcoma should be regarded as a high grade neoplasm,[7,15,17] some believing that histologic grade was an unreliable prognostic variable in this tumor.[7] However, the long survival reported in the present series together with evidence of minimal cytological atypia in these tumors supports the notion of a histologically low grade variant of osteosarcoma with a clinical behavior that is commensurate with this grade.

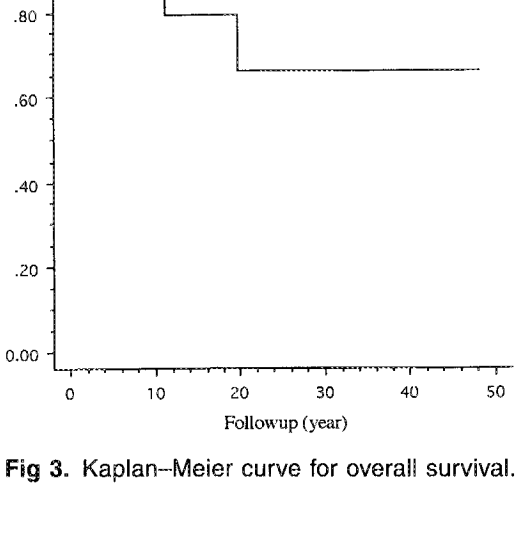

Fig 3. Kaplan–Meier curve for overall survival.

An early report from this institution first recognized the existence of an intramedullary osteogenic sarcoma that was so well differentiated as to be confused with benign processes.[21] Since that time, other sporadic reports have enhanced existing knowledge regarding this rare variant.[2,5,8,9,13,19,20,23] Low grade central osteogenic sarcoma represents <2% of all osteosarcomas.[4] It differs from conventional osteosarcoma by the older age at onset and the equality at which both genders are afflicted. There was a predisposition for it to arise at the ends of long bones; none of the 20 patients from the Mayo Clinic in this series showing involvement of a flat bone as the primary site. Like conventional osteosarcoma, the femur and tibia were the most common sites. Unlike the more aggressive conventional lesions, a prolonged premorbid history of pain was typical of this tumor, with a mean symptom duration of 4 years in the authors' series, extending up to 15 years. Tumors may also present as a mass, although this was uncommon in the authors' patients.

The variable and bland-appearing radiologic features of this condition are potential sources for misdiagnosis. As a result, an initial diagnosis of a benign process was made in 2 of 12 patients seen at this institution, and 5 of 8 patients diagnosed elsewhere. Trabeculation and sclerosis were common findings which reflect the indolent nature of this tumor, and which may lead to a benign diagnosis in the first instance. The extension into the epiphysis may confuse low grade central osteosarcomas with benign processes such as giant cell tumors, aneurysmal bone cysts, simple bone cysts, fibrous dysplasia, nonossifying fibroma, and even chondromyxoid fibroma. In most

cases, however, at least a small region will show poor margination, breach of the cortex, soft tissue shadows, and calcification, as well as periosteal reaction that should strengthen a suspicion of malignancy.

The histologic diagnosis can be difficult. Fibrous dysplasia was the original diagnosis in 3 patients in this series. If the histology suggests fibrous dysplasia but the radiographs are inconsistent with that diagnosis, low grade osteosarcoma should be considered. Permeation of marrow fat and other preexisting structures is the most helpful feature separating low grade osteosarcoma from fibrous dysplasia. The subtle cytologic atypia seen in low grade central osteosarcoma is too subjective to be reliable. The neoplastic cells in osteosarcoma have long spindly nuclei whereas those of fibrous dysplasia are plump and short. Nonossifying fibroma[11] was the initial diagnosis for 3 patients, and the radiologic appearance of low grade central osteosarcoma may be so similar as to make differentiation from the former difficult. In this case, the presence of bone formation, the absence of cytoplasmic deposition of hemosiderin, and the absence of lipid-laden cells helped to exclude this diagnosis. Chondromyxoid fibroma[10] was another primary diagnosis that was made. The radiographic appearance and the observation of fibrous bundles intermingled with areas of cartilaginous differentiation and myxoid degeneration may be confusing. The presence of a dominant spindle cell stroma, synthesis of osteoid, and radiographic evidence of destruction should direct the diagnosis toward one of malignancy. The histologic features of giant cell tumor[12] can readily differentiate this diagnosis from low grade central osteosarcoma.

Local recurrence was a key feature of low grade central osteosarcoma. This was, in almost all cases, a result of inadequate surgical margins and highlights the necessity of making an accurate diagnosis if local control is to be achieved. The high number of incorrect initial diagnoses (9 of 20 patients) reiterates the difficulty that may be encountered in reaching the true diagnosis. Sundaram et al[20] reported a similar result after curettage of low grade central osteosarcoma, and the excellent result after amputation for local recurrence. Although amputation successfully controlled primary and recurrent tumors in the authors' patients, the availability of modern imaging modalities and current reconstructive techniques should make limb salvage surgery a definite option in patients with this condition. Unlike most sarcomatous lesions, local recurrence after intralesional surgery of low grade central osteosarcoma was delayed a median period of 3 years, and for 1 patient as long as 14 years. This reflects the rather indolent nature of low grade central osteosarcoma and suggests that even with inadequate treatment long disease-free survival is possible.

The indolent nature of this neoplasm and its salvageability after recurrence, however, does not justify intralesional surgery of the primary tumor because recurrences may exhibit a higher grade or be dedifferentiated. Iemoto et al[9] described the first reported case of low grade central osteosarcoma with foci of dedifferentiation at initial presentation. The patient died from disseminated metastases, and the microscopic appearance of these metastases was identical to the anaplastic histology of the original tumor. For parosteal ostegenic sarcoma, which is histologically similar to low grade central osteosarcoma and which also has a more favorable survival than conventional osteogenic sarcoma, dedifferentiation has been shown to be a negative prognostic factor.[22] The deaths of 2 of the authors' patients from metastasis after local recurrence and the experience of Iemoto et al[9] and Wold et al[22] underscore the attendant risks of high grade osteosarcomas developing from local recurrence. Although surgery alone appears effective for this variant of osteosarcoma, patients in whom higher grade local recurrences or dedifferentiated lesions develop, may represent a high risk group and, as such, may qualify as candidates for adjuvant chemotherapy.

Low grade central osteosarcoma is a distinct variety of osteosarcoma that is eminently treatable by surgery with wide margins alone. Good local control is associated with an excellent long-term survival. Confusion with benign processes in bone often leads to local recurrence because of inadequate surgical margins. Histology and radiology are complementary for confirming the diagnosis, although the diagnosis must be sought. Dedifferentiation is an uncommon but potentially fatal sequel to local recurrence. Late metastases can occur and the continued decline in survival even after 10 years suggests that long-term followup is important to determine survival rates.

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